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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE **RECEIVED**

Applicants: Anna Marie Pyle et al.

SEP 20 2001

Serial No.: 09/492,954

Examiner: C.B. Wilder
TECH CENTER 1600/2900

Filed : January 27, 2000

Art Unit: 1655

For : ASSAYS FOR EVALUATING THE FUNCTION OF RNA
HELICASES

1185 Avenue of the Americas
New York, New York 10036
September 10, 2001

Honorable Commissioner of Patents and Trademarks
Washington, D.C. 20231

SIR:

**COMMUNICATION IN REPLY TO MARCH 14, 2001 OFFICE ACTION AND
PETITION FOR A THREE-MONTH EXTENSION OF TIME**

This Communication is submitted in reply to the March 14, 2001 Office Action issued by the U.S. Patent and Trademark Office in connection with the above-identified application. A reply to the March 14, 2001 Office Action was originally due June 14, 2001. Applicants hereby request a three-month extension of time from June 14, 2001 to September 14, 2001. The fee of FOUR HUNDRED AND FORTY FIVE DOLLARS (\$445.00) is enclosed herewith. Therefore, reply to the March 14, 2001 Office Action is now due September 14, 2001 and this Communication is being timely filed.

Withdrawal of Previous Objections and Rejections

The Examiner withdrew the objections to the drawings and the specification in view of Applicant's previous amendment. In addition, the Examiner withdrew the rejections of claims 1-6 under 35 U.S.C. §112 second paragraph as being indefinite in

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view of Applicant's amendment of the claims and arguments.

Rejection Under 35 U.S.C. § 103

The Examiner rejected claims 1-8 under 35 U.S.C. §103(a) as being unpatentable over Shuman (Proc. Natl. Acad. Sci. USA, November 1992), in view of Bjornson et al. (Biochemistry, December 1994) and further in view of Eggleston et al. (Nucleic Acids Research, April 1996).

In response to applicants' previous arguments asserting that there is no suggestion to combine the references, the Examiner stated that in this case, the primary reference of Shuman teaches detecting the release of ssRNA from an RNA duplex comprising the use of RNA helicase under conditions which permits the release wherein the RNA duplex comprises multiple radiolabels and detection is monitored using gel electrophoresis. The Examiner stated that the secondary reference of Bjornson et al. teaches the use of fluorescent labels in energy transfer assays to monitor the release and unwinding of ssDNA from DNA duplexes using helicases. The Examiner stated that the reference of Bjornson et al. teach several advantages of using fluorescent based assays to monitor unwinding of DNA instead of the methods using radiolabels and electrophoresis. The Examiner stated that Bjornson et al. teach the fluorescent based study will greatly facilitate the detailed kinetic studies that are needed to understand the mechanisms by which helicases (implying both RNA and DNA helicases) carry out their function. The Examiner stated that further motivation for

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using the fluorescent labels in the method of detecting release of RNA by RNA helicases (implying both RNA and DNA helicases) carry out their function. The Examiner stated that further motivation for using the fluorescent labels in the method of detecting release of RNA by RNA helicases is provided in the teachings of Eggleston et al. that fluorescent based assays can be readily adapted for use with DNA helicases, RNA helicases and any other enzyme that acts on nucleic acids to monitor DNA or RNA unwinding. The Examiner stated that Eggleston further teach that fluorescent based methods are advantageous for detailed studies of kinetic mechanisms because they provide continuous data in real time. Therefore, the Examiner stated that in contrast to Applicant's arguments, one of ordinary skill in the art would expect with a reasonable expectation of success that the use of fluorescent labels instead of radiolabels could be used to monitor the unwinding and release of RNA from RNA duplexes. The Examiner stated that Applicant's arguments did not provide sufficient evidence to overcome the prior art rejection under 103(a). The Examiner stated that accordingly the rejection is maintained.

The Examiner stated that regarding claim 2, Shuman discloses wherein the conditions which permit the RNA helicase to unwind the RNA duplex and release the single stranded RNA comprise the presence of ATP and a divalent cation, e.g., Mg^{2+} , Co^{2+} , and Mn^{2+} (page 10936, col. 1, lines 40-52).

The Examiner stated that regarding claims 3 and 4, Bjornson et al. teach wherein a label is present at the 3' end of the first

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strand of the DNA and a different label is attached to the second strand of the DNA at the 5' end and the luminescent energy pattern results from the interaction of luminescent energy released from the two different labels (page 14309 col. 2, lines 1-28 see also Figure 1).

The Examiner stated that regarding claim claim 5, Bjornson teach wherein the two labels comprise fluorophors and the second label absorbs luminescent energy released from the first fluorophor (page 14309, Figure 1).

The Examiner stated that regarding claim 6, Bjornson et al. teach wherein the first label is fluorescein (donor) and the second label is hexachlorofluorescein (acceptor) (page 14309, Figure 1 and 14310, Figure 2). The Examiner stated that the choice of a first and second label would have been determined by the skilled artisan based on commercial availability, experimental procedures and desired results.

The Examiner stated that regarding claim 7, Bjornson et al., disclose a method of measuring the rate of release of DNA from a DNA duplex which comprise detecting whether single stranded DNA is released from the duplex at predetermined time intervals and determining the rate of release of the single stranded DNA from the duplex (page 14310, Figure 2 and col. 2, first and second full paragraphs).

The Examiner stated that regarding claim 8, Shuman discloses a method of determining whether a compound is capable of

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modulating the release of a single stranded RNA from an RNA duplex by an RNA helicase which comprise detecting the release of the single stranded RNA from the RNA duplex, wherein the compound (AMPPNP or AMPPCP) is added to the mixture comprising the RNA helicase, RNA duplex and label (page 10937, figure 5).

In reply, applicants maintain their traversal of the rejection and submit that there is no motivation to combine the cited references. In addition, applicants submit that the combination of Shuman, Bjornson et al. and Eggleston et al. do not make the claimed invention obvious.

Applicants submit that there is no motivation to combine the references absent applicants' invention and that the Examiner has used hindsight to arrive at the combination of references. The Shuman reference utilizes native gel electrophoresis to analyze the extent of RNA unwinding (see Figure 4 of Shuman et al.) and does not teach or suggest the use of fluorescent labels capable of producing a luminescent energy pattern. Shuman et al. makes no reference to and does not suggest subjecting an admixture of RNA helicase, RNA duplex which comprises an RNA having a label, to conditions which not only permit the RNA duplex to unwind, but also to allow the first label to produce luminescent energy (see step (b) of claim 1 of the subject application). Finally, there is no teaching or suggestion in Shuman et al. to detect a change in a luminescent energy pattern as recited in step (c) of claim 1. Shuman et al. rely exclusively on the native gel electrophoresis analysis method and there is no indication at all that a different method is

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necessary, let alone the method of the presently claimed invention. Clearly, Shuman et al. believed the methods described in their paper to be sufficient based upon the detailed analysis provided on page 10937, last paragraph to 10938, column 1, line 4. Therein, Shuman et al. discuss the mobility shift assay and provide a calculation to determine the number of molecules of RNA displaced per molecule of input enzyme. This specific calculation indicates that the authors do not want for a more accurate method or a method which would allow a more detailed analysis.

The Examiner relies on the teaching of Eggleston et al. "that fluorescent based assays can be readily adapted for use with DNA helicases, RNA helicases and other enzymes that act on nucleic acid to monitor nucleic acids unwinding." See page 5, lines 5-7 of the March 14, 2001 Office Action. Applicants submit that this statement is clearly **an invitation to try to adapt** the protocols described in the Eggleston paper to other uses. Eggleston et al. recite other types of continuous fluorometric assays on page 1179, column 2, lines 22-36. Applicants point out that Eggleston et al. explicitly state that "each of the assays described above has merits and limitations." See page 1179, column 1, line 36. Some limitations noted by Eggleston et al. are that the assay is non-continuous or that "considerable manipulation" is required before results are obtained. Furthermore, Eggleston et al. is clear to say that "it would **theoretically** be possible to monitor the process of DNA or RNA unwinding by" (Emphasis added, see page 1180, 2nd column, 2nd paragraph, last line.) The authors are emphasizing the

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difference between what theoretically could be possible and what is obvious or suggested by their results. All of the experimental description of Eggleston et al. focuses on DNA and there is no disclosure of RNA unwinding at all. Finally, in the Discussion section on page 1184, column 2, the authors state that the assay could be applicable to a variety of helicases "provided that a suitable, non-inhibitory dye ligand is selected." The authors go on to state on page 1185, column 1 that "since the choice of a non-inhibitory dye appropriate for use with a new helicase **will be empiracal**...." (Emphasis added.) Therefore, applicants submit that the statements upon which the Examiner relies to provide motivation are not sufficient.

Applicants would like to direct the Examiner's attention to *In re Rouffet*, 47 USPQ2d 1453 (Fed. Cir. 1998) which holds that in order for an Examiner to combine references and reject claims, there must be some motivation to combine the references. Without such motivation, the Court implied an improper reliance on hindsight. The Court stated, in pertinent part:

if such a rote invocation could suffice to supply a motivation to combine, the more sophisticated scientific fields would rarely, if ever, experience a patentable technical advance. Instead, in complex scientific fields, the Board could routinely identify the prior art elements in an application, invoke the lofty level of skill, and rest its case for rejection. To counter this potential weakness in the obviousness construct, the suggestion to combine requirement stands as a critical safeguard against hindsight analysis and

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rote application of the legal test for
obviousness.

See 47 USPQ2d at 1458. Applicants submit, in view of the discussion above and the pertinent case law, the Examiner has not provided motivation to combine the three cited references.

Nevertheless, even if the three references are combined, applicants submit that the combination does not provide one of ordinary skill in the art a reasonable expectation of success of carrying out the claimed invention. Clearly, the statements of Eggleston et al. as to the use of the disclosed method for use with RNA helicases is, at most, an invitation for others to try. The combination of the cited references, which applicants maintain is based on an impermissible hindsight analysis, does not render the claimed invention obvious.

In view of the above discussion, applicants request that the Examiner reconsider and withdraw this ground of rejection.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicant's undersigned attorney invites the Examiner to telephone at the number provided.

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No fee, other than the \$445.00 extension of time fee, is deemed necessary in connection with the filing of this Communication. However, if any fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,

Jane M. Love

I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to:
Hon. Commissioner of Patents and Trademarks, Washington, D.C. 20231.

Jane M. Love 9/10/01
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